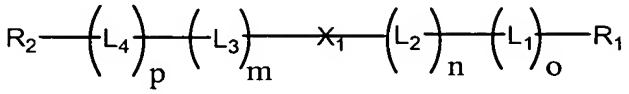
We claim:

1. An oligonucleotide prodrug of the formula (I):



(I)

wherein:

R_1 and R_2 are independently H or a polymer residue;

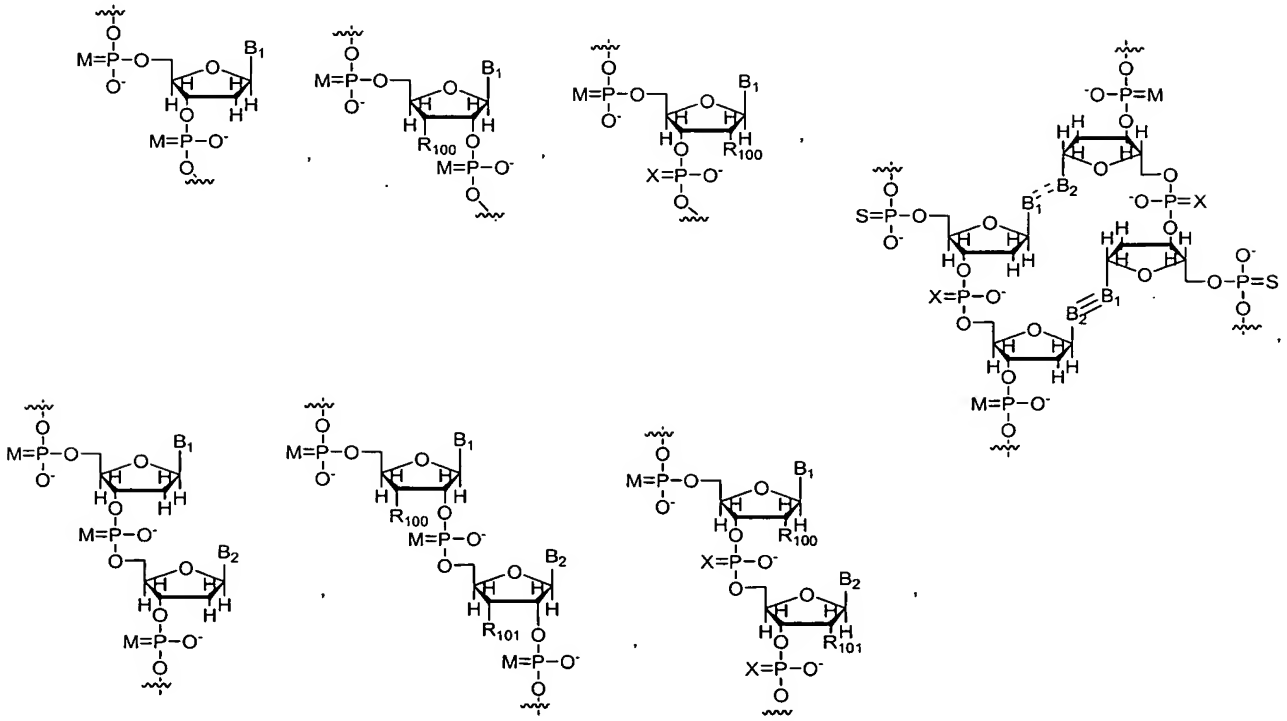
L_1 and L_4 are independently selected releasable linking moieties;

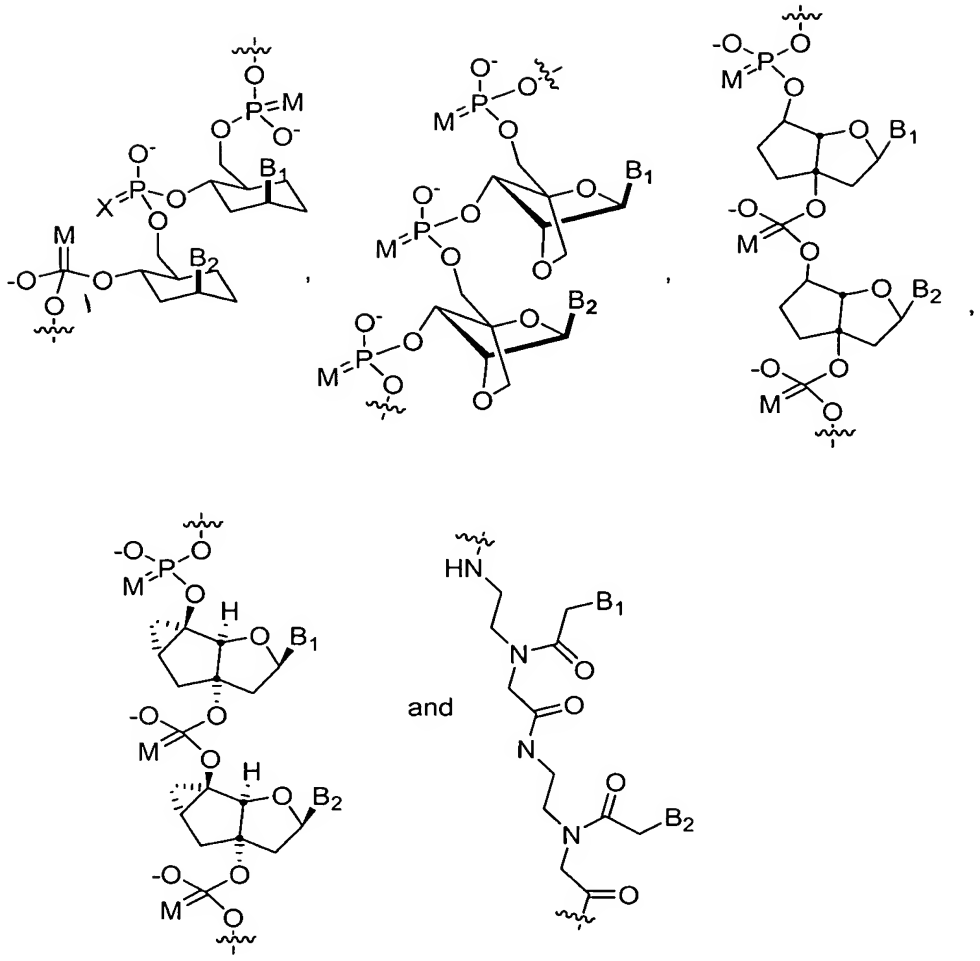
L_2 and L_3 are independently selected spacing groups;

X_1 is a nucleotide or an oligonucleotide residue;

m, n, o and p are independently zero or a positive integer, provided that either (o + n) or (p + m) ≥ 2.

2. The prodrug of claim 1, wherein said nucleotide is selected from the group consisting of





wherein

M is O or S;

B_1 and B_2 are independently selected from the group consisting of A (adenine), G (guanine), C (cytosine), T (thymine), U (uracil) and modified bases;

R_{100} and R_{101} are independently selected from the group consisting of H, OR' where R' is H, a C_{1-6} alkyl, substituted alkyls, nitro, halo and aryl

3. The prodrug of claim 1, wherein said oligonucleotide is contains from about 10 to about 1000 nucleotides.

4. The prodrug of claim 1, wherein M is S.

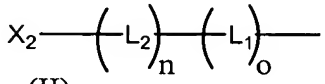
5. The prodrug of claim 1, wherein the oligonucleotide is a phosphorthioate oligonucleotide.

6. The prodrug of claim 1, wherein said oligonucleotide residue is an antisense oligonucleotide residue or oligodeoxynucleotide residue.

7. The prodrug of claim 6, wherein said antisense oligonucleotide residue or oligodeoxynucleotide residue is selected from the group consisting of, oligonucleotides and oligodeoxynucleotides with phosphorodiester backbones or phosphorothioate backbones, LNA, PNA, tricyclo-DNA, decoy ODN, RNAi, ribozymes, spiegelmers, and CpG oligomers.

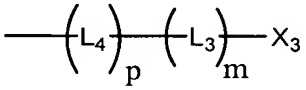
8. The prodrug of claim 6, wherein said antisense oligonucleotide has a sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, and SEQ ID NO: 4, wherein X of SEQ ID NO: 4 is any compatible nucleotide.

9. The prodrug of claim 1, wherein at least one of R_1 and R_2 is a polymeric residue having a capping group A, selected from the group consisting of OH, NH_2, SH, CO_2H, C_{1-6} alkyls,



(II)

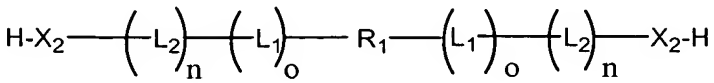
and



(III)

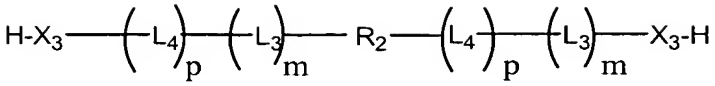
wherein X_2 and X_3 are independently selected nucleotide or oligonucleotide residues.

10. A prodrug of claim 9, selected from the group consisting of:

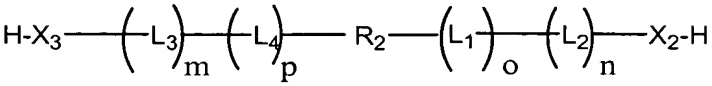


(i)

bis-3'-oligonucleotide,

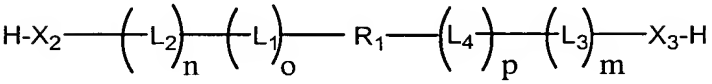


(ii)
bis-5'-oligonucleotide,



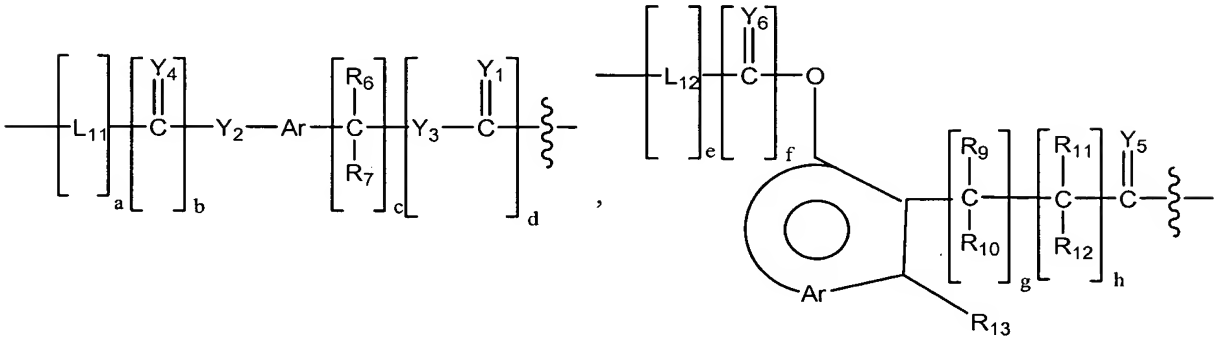
(iii)
bis-5', 3'-oligonucleotide,

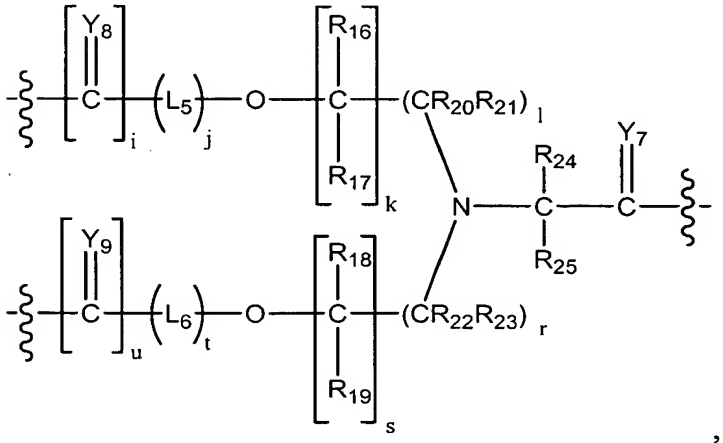
and

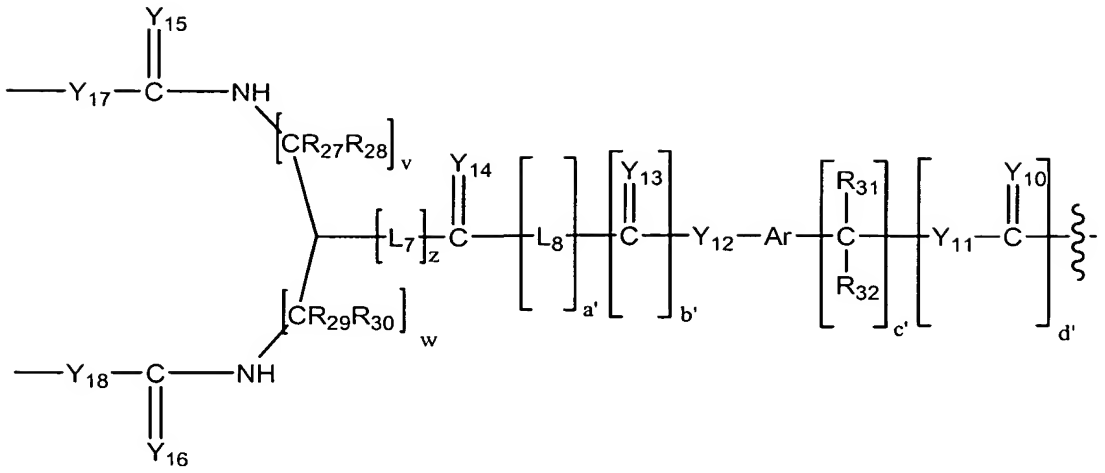


(iv)
bis-3', 5'-oligonucleotide.

11. The prodrug of claim 1 wherein L_4 is selected from the group consisting of:







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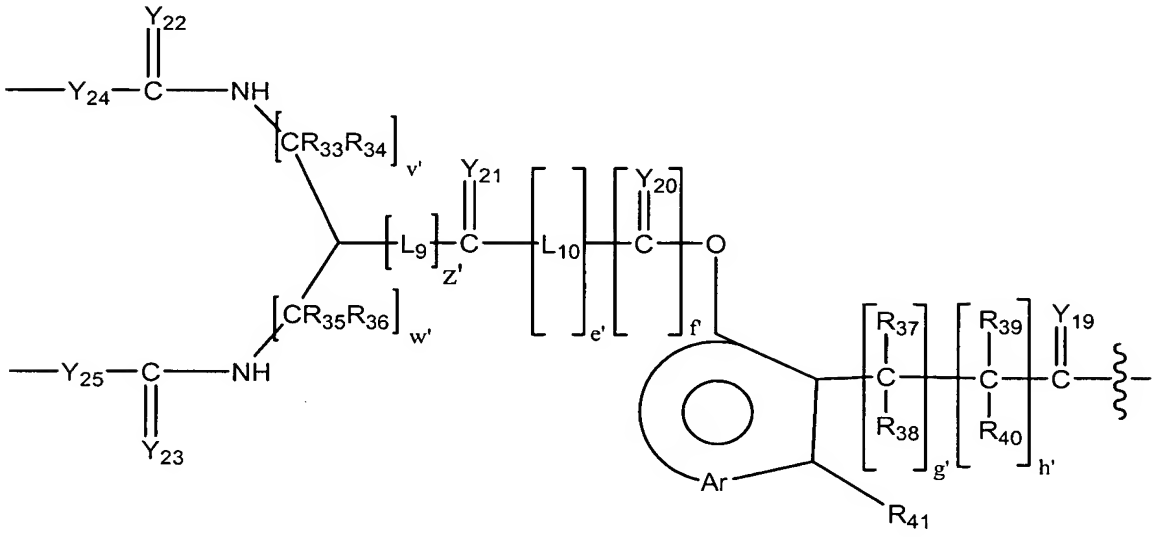


wherein:

Y_{1-25} are independently selected from the group consisting of O, S or NR_9;

R_{6-7}, R_{9-13}, R_{16-25}, and R_{27-41} are independently selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{3-12} branched alkyls, C_{3-8} cycloalkyls, C_{1-6} substituted alkyls, C_{3-8} substituted cyloalkyls, aryls, substituted aryls, aralkyls, C_{1-6} heteroalkyls, substituted C_{1-6} heteroalkyls, C_{1-6} alkoxy, phenoxy and C_{1-6} heteroalkoxy;

Ar is a moiety which forms a multi-substituted aromatic hydrocarbon or a multi-substituted heterocyclic group;

L_{5-12} are independently selected bifunctional spacers;

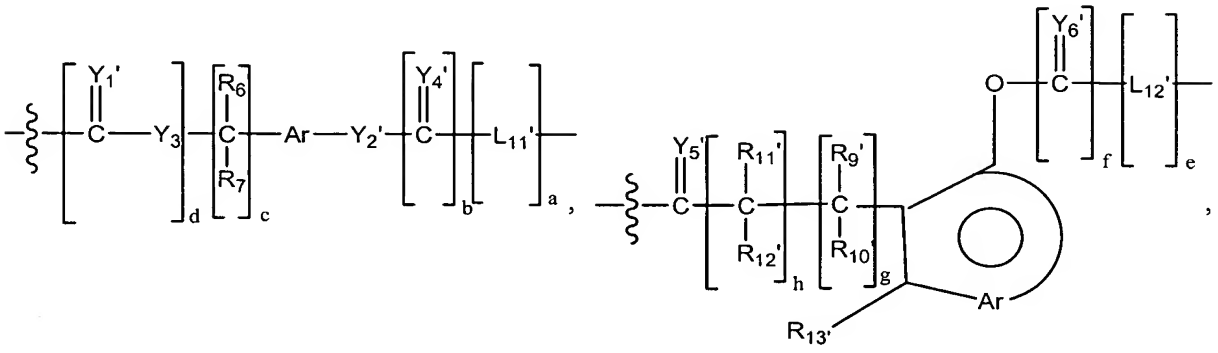
Z is selected from among moieties actively transported into a target cell, hydrophobic moieties, bifunctional linking moieties and combinations thereof;

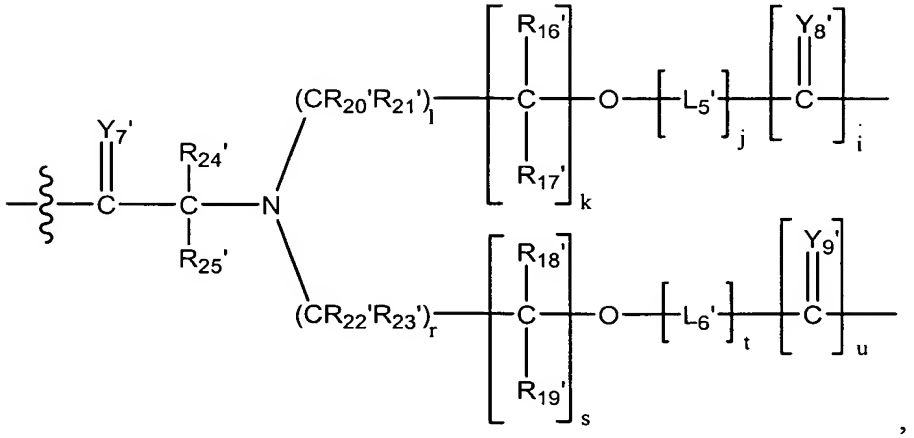
c, h, k, l, r, s, v, w, v', w', c', and h' are independently selected positive integers;

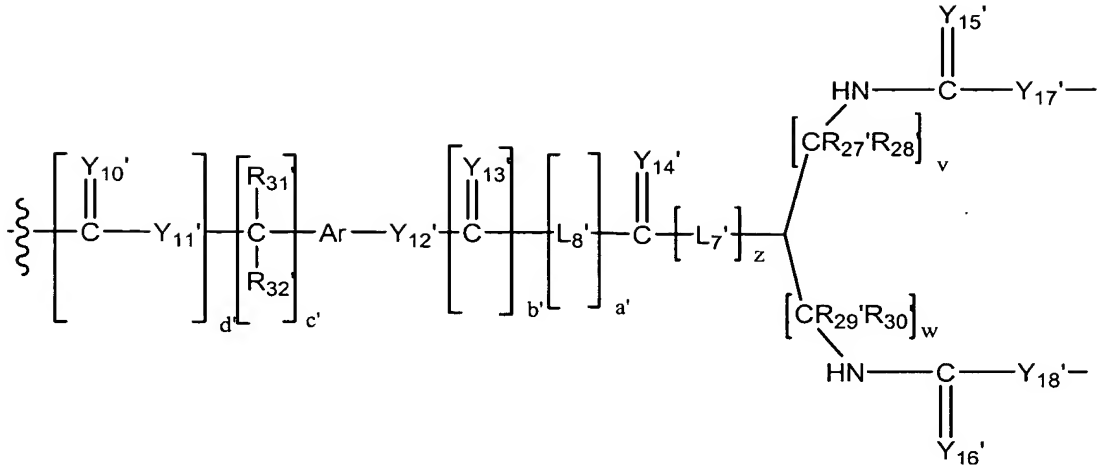
a, e, g, j, t, z, a', z', e' and g' are independently either zero or a positive integer; and

b, d, f, i, u, q, b', d' and f' are independently zero or one.

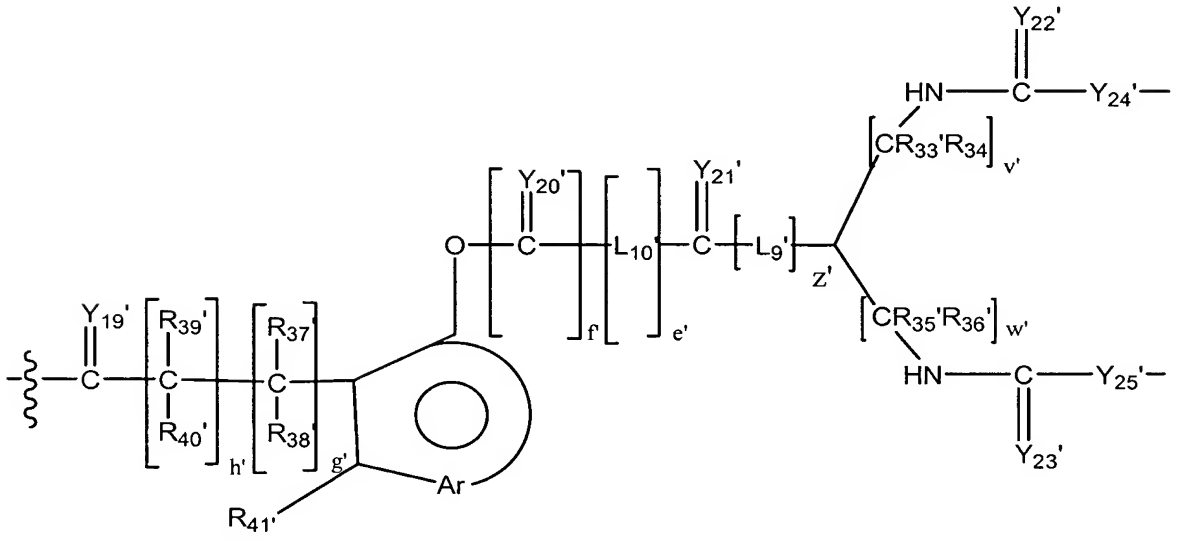
12. The prodrug of claim 1 wherein L_1 is selected from the group consisting of:







and



wherein,

$Y_{1'}$-$Y_{25'}$ are independently selected from the group consisting of O, S or NR_9;

$R_{6'-7'}$, $R_{9'-13'}$, $R_{16'-25'}$, and $R_{27'-41'}$ are independently selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{3-12} branched alkyls, C_{3-8} cycloalkyls, C_{1-6} substituted alkyls, C_{3-8} substituted cyloalkyls, aryls, substituted aryls, aralkyls, C_{1-6} heteroalkyls, substituted C_{1-6} heteroalkyls, C_{1-6} alkoxy, phenoxy and C_{1-6} heteroalkoxy; and

$L_{5'-12'}$ are independently selected bifunctional spacers.

13. The prodrug of claim 1 wherein R_{1-2} are each polyalkylene oxides.

14. The prodrug of claim 1 wherein R_{1-2} are each polyethylene glycols.

15. The prodrug of claim 1 wherein R_{1-2} are independently selected from the group consisting of:

$$J\text{- }O\text{-}(CH_2CH_2O)_{n'}\text{-}$$
$$J\text{-}O\text{-}(CH_2CH_2O)_{n'}\text{-}CH_2C(O)\text{-}O\text{-},$$
$$J\text{-}O\text{-}(CH_2CH_2O)_{n'}\text{-}CH_2CH_2\ NR_{48}\text{-},$$
$$J\text{-}O\text{-}(CH_2CH_2O)_{n'}\text{-}CH_2CH_2\ SH,$$
$$\text{-}O\text{-}C(O)CH_2\text{-}O\text{-}(CH_2CH_2O)_{n'}\text{-}CH_2C(O)\text{-}O\text{-},$$
$$\text{-}NR_{48}CH_2CH_2\text{-}O\text{-}(CH_2CH_2O)_{n'}\text{-}CH_2CH_2\ NR_{48}\text{-},$$
$$\text{-}SHCH_2CH_2\text{-}O\text{-}(CH_2CH_2O)_{n'}\text{-}CH_2CH_2\ SH\text{-},$$

wherein

n' is the degree of polymerization;

R_{48} is selected from the group consisting of hydrogen, C_{1-6}alkyls, C_{3-12} branched alkyls, C_{3-8} cycloalkyls, C_{1-6} substituted alkyls, C_{3-8} substituted cyloalkyls, aryls substituted aryls, aralkyls, C_{1-6} heteroalkyls, substituted C_{1-6}heteroalkyls, C_{1-6} alkoxy, phenoxy and C_{1-6} heteroalkoxy; and

J is a capping group.

16. The prodrug of claim 1, wherein R_{1-2} are independently

$$\text{- }O\text{-}(CH_2CH_2O)_x\text{ –}$$

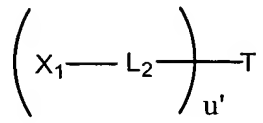
wherein x is a positive integer selected so that the weight average molecular weight is at least about 2,000 Da to about 136,000 Da.

17. The prodrug of claim 1, wherein R_{1-2} independently have a weight average molecular weight of from about 3,000 Da to about 100,000 Da.

18. The prodrug of claim 1, wherein R_{1-2} independently have a weight average molecular weight of from about 5,000 Da to about 40,000 Da.

19. The prodrug of claim 8, wherein said antisense oligonucleotide is oblimersen (SEQ ID NO: 1).

20. An oligonucleotide prodrug of the formula:



(v)

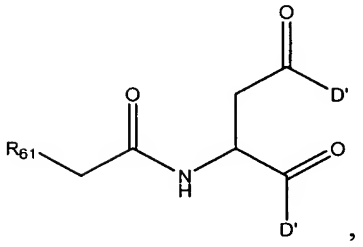
wherein:

L_2 is a spacing group;

X_1 is a nucleotide or an oligonucleotide residue;

u' is a positive integer; and

T is a member of the group consisting of:



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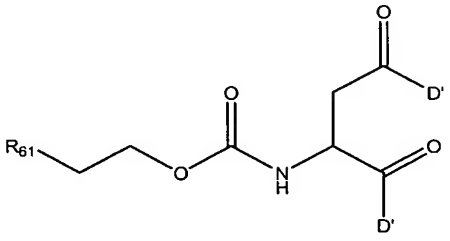

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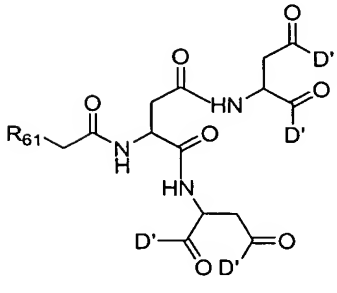

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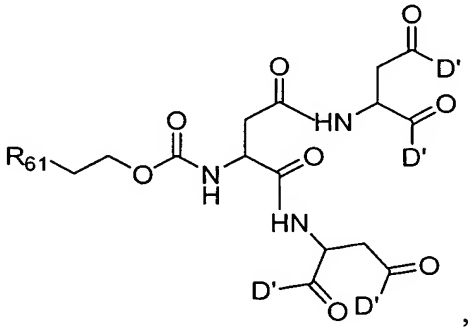
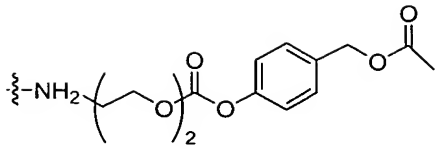
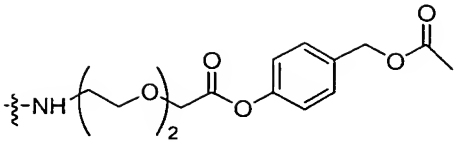
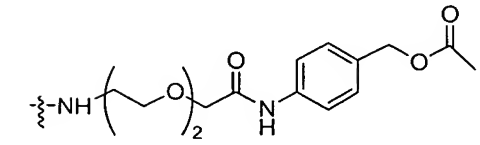
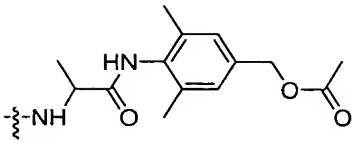
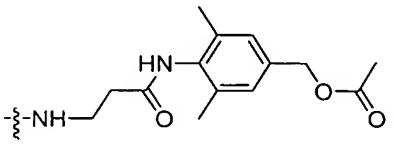
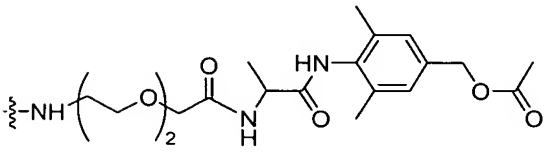
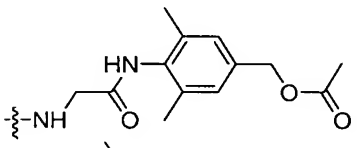
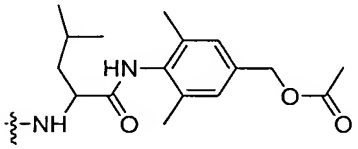
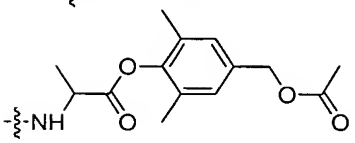
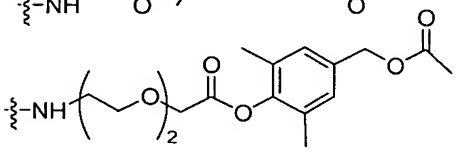
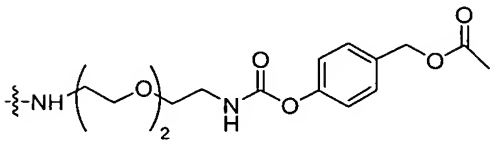
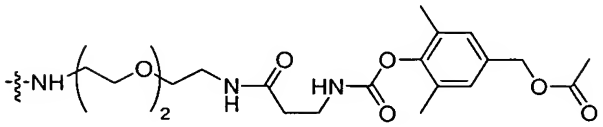
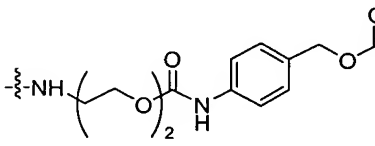
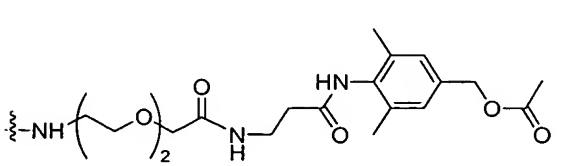


,

wherein:

D' is one of

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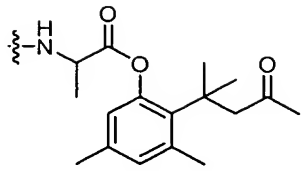
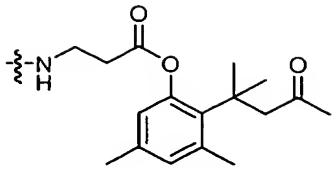
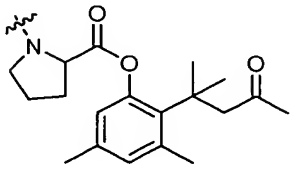
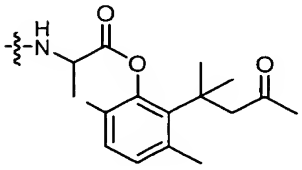
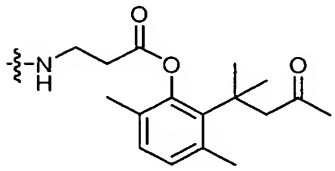
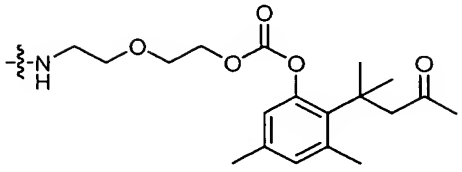
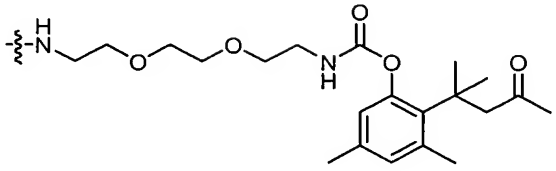
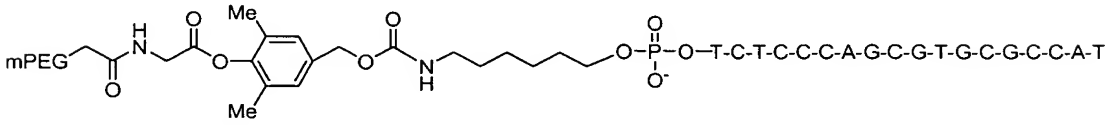







and 

and wherein R_{61} is a polymer residue.

21. A compound of claim 1 selected from the group consisting of:



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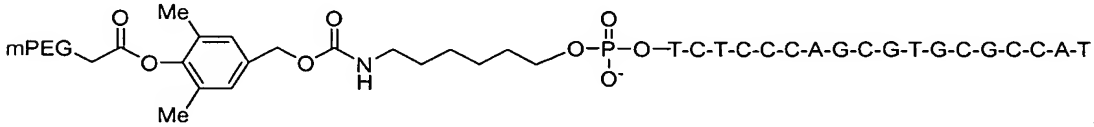

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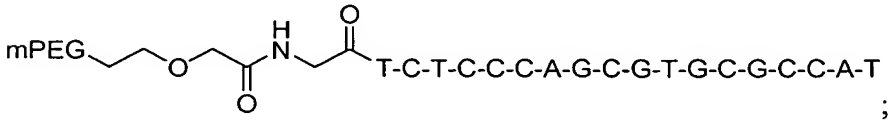
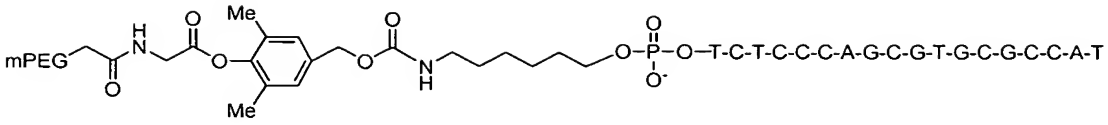


;

and



all of which comprise an oligonucleotide of SEQ ID NO: 1.

22. A method of making a prodrug comprising:

reacting a compound of the formula:

R_2-L_4-leaving group

with a compound of the formula:

H-L_3-X_1

under conditions sufficient to form a prodrug of the formula

R_2-L_4-L_3-X_1 ,

wherein:

R_2 is a polymer residue;

L_4 is a releasable linking moiety;

L_3 is a spacing group;

X_1 is a nucleotide or an oligonucleotide residue.

23. A method of treating a mammal, comprising administering to a mammal in need of such treatment an effective amount of a compound of claim 1.

24. The method of claim 23, wherein the mammal is being treated for cancer.

25. The method of claim 23, wherein X_1 is an antisense oligonucleotide.

26. The method of claim 23 wherein the mammal is also treated with a second anticancer agent that is administered simultaneously or sequentially with the oligonucleotide prodrug.